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Ray W. Wood

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EXAMINER

ALSTRUM ACEVEDO, JAMES HENRY

ART UNIT

PAPER NUMBER

1616

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PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 09/577,489	<b>Applicant(s)</b> WOOD ET AL.	
	<b>Examiner</b> JAMES H. ALSTRUM- ACEVEDO	<b>Art Unit</b> 1616	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 10 February 2012.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on \_\_\_\_; the restriction requirement and election have been incorporated into this action.
- 4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 5) ☒ Claim(s) 28-36,39,40,42,43,51-60 and 64-74 is/are pending in the application.
- 5a) Of the above claim(s) \_\_\_\_ is/are withdrawn from consideration.
- 6) ☐ Claim(s) \_\_\_\_ is/are allowed.
- 7) ☒ Claim(s) 28-36,39,40,42,43,51-60 and 64-74 is/are rejected.
- 8) ☐ Claim(s) \_\_\_\_ is/are objected to.
- 9) ☐ Claim(s) \_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 10) ☐ The specification is objected to by the Examiner.
- 11) ☐ The drawing(s) filed on \_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 12) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                                | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. ____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date ____. | 6) <input type="checkbox"/> Other: ____.  |

**DETAILED ACTION**

**Claims 28-36, 39-40, 42-43, 51-60, and 64-74 are pending.** Applicants previously cancelled claims 1-27, 37-38, 41, 44-50, and 61-63. Applicants' reply did not newly amend or cancel any claims. Receipt and consideration of Applicants' remarks/arguments and § 1.132 declaration (Dr. Liversidge Declaration) submitted on February 10, 2012 are acknowledged. All rejections/objections not explicitly maintained in the instant office action have been withdrawn per Applicants' claim amendments and/or persuasive arguments.

***Priority***

**The effective filing date of the instant application is February 24, 1995.**

***Election/Restrictions***

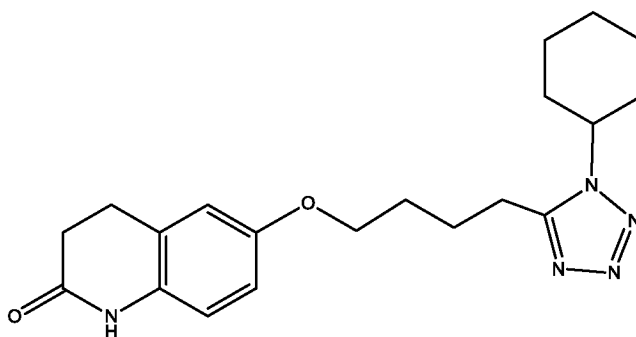
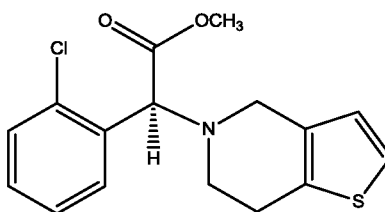
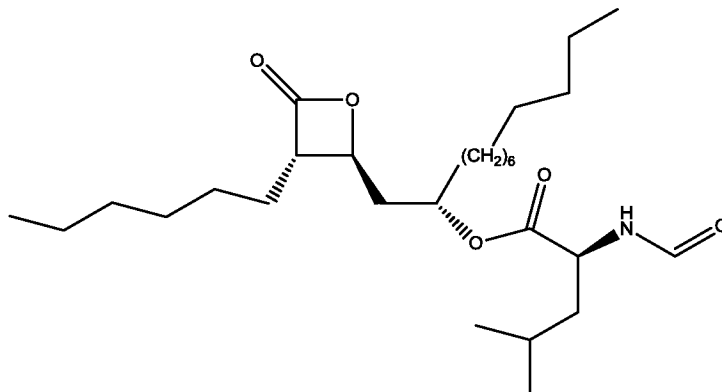
The species elections for (i) asthma as the respiratory disease in a mammal and (ii) corticosteroids as the elected therapeutic agent are maintained and remain in effect.

***Specification***

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

***Consideration of Dr. Gary G. Liversidge's 1.132 Declaration***

Dr. Gary Liversidge ("Dr. Liversidge") opines in his declaration ("Liversidge declaration") that obtaining stable nanoparticulate formulations of functionally equivalent drugs is challenging and unpredictable. Liversidge declaration at ¶ 4. Dr. Liversidge compares the success of obtaining nanoparticulate formulations of cilostazol, an anti-

**Cilostazol****Clopidogrel bisulphate****Orlistat**

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plaque agent, *Id.*, to the failed attempts of obtaining nanoparticulate formulations of clopidogrel bisulphate, an antiplaque agent, *Id.* Dr. Liversidge also notes that attempts of obtaining nanoparticulate formulations of orlistat, an anti-obesity drug, were also unsuccessful. *Id.* at ¶¶ 17-20. It is noted that the compounds compared by Dr. Liversidge are structurally unrelated and do not share a common core structure, as evidenced by the chemical structures of cilostazol, clopidogrel bisulphate, and orlistat shown above.

Dr. Liversidge also cites and briefly discusses recent general reviews of nanoparticulate pharmaceutical technologies by Banavath et al. (“Banavath”; Exhibit 3 in the Liversidge declaration), *Id.* at ¶¶ 21-22, and Wu et al. (“Wu”), *Id.* at ¶¶ 23-24. Regarding Banavath, Dr. Liversidge only refers to the disadvantages of various methods of obtaining nanosuspensions and ignores or fails to mention the recognized advantages of these very same methods identified by Banavath, such as the recognized advantages of media milling: (i) its suitability for use with drugs that are poorly soluble in both aqueous and non-aqueous media (ii) the existence of little batch-to-batch variation, and (iii) the high flexibility in handling large quantities of drugs (See Table 2 on page 4 of Banavath). The method used by the below cited Liversidge reference, U.S. Patent No. 5,145,684 (“the ‘684 patent”), is equivalent to the media milling described by Banavath. Banavath begins the conclusion of the review by stating on page 9, “Nanosuspensions are chiefly seen as vehicles for administering poorly water soluble drugs [and] have been [sic] **largely solved** the dissolution problems to improve drug absorption and bioavailability.” Thus, contrary to Dr. Liversidge’s implied argument, the ordinary skilled artisan would be encouraged to consider nanosuspensions techniques and would have had a reasonable, although not an absolute, expectation of success.

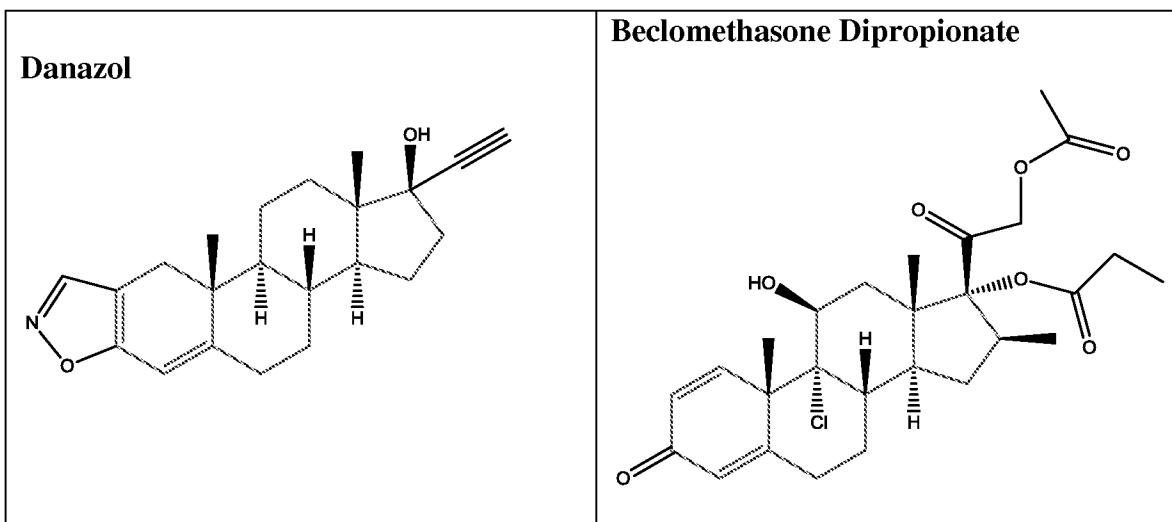
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Regarding Wu, Dr. Liversidge emphasizes Wu's statements that (i) it remains challenging to obtain nanoparticulate active agent compositions that are chemically and physically stable, because stability is affected by many factors; (ii) lack of a fundamental understanding of the interaction between the surface stabilizer and the active agent nanoparticles; (iii) the process of selecting an appropriate surface stabilizer having an appropriate stabilizer anchoring tail is burdensome; (iv) the lack of predictability due to the lack of any correlation between the physicochemical properties of the active agent; and (v) the lack of an efficient throughput screening technique to identify suitable surface stabilizer. The cited statements for Wu support the notion that there is no absolute expectation of success in obtaining nanoparticulate formulations of an arbitrary drug candidate selected at random. But, Wu does not address the factual circumstances considered in the below rejection under § 103(a) and cannot be the basis of alleged lack of a reasonable expectation of successfully obtaining nanoparticulate formulations of beclomethasone, a corticosteroid.

Thus, Dr. Liversidge's opinion that it is unpredictable whether a specific drug can successfully be formulated into nanoparticulate formulations when comparing functionally equivalent drugs (i.e. drugs known to be suitable for the same purpose) that impliedly do not share a common core structure may be a reasonable conclusion in the absence of any additional information and is supported by the tabulated data on pages 4-8 of his declaration as well as his citation to a post-filing reference by Jinno et al. on page 2 of his declaration. Nonetheless, Dr. Liversidge's declaration does not address the predictability or lack thereof of obtaining nanoparticulate formulations of drugs sharing the same or substantially similar core structure, such as would be the case when

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comparing the success or failure of obtaining nanoparticulate formulations of different corticosteroids or different steroids that are taught by the prior art and post-filing art as being suitable for obtaining nanoparticulate formulations (e.g. Liversidge et al.: (1) U.S. Patent No. 5,145,684 and (2) U.S. Patent No. 8,003,127). Corticosteroids are steroids. The below cited '684 patent specifically identifies corticosteroids as being suitable for preparation of nanoparticulate formulations and indicates a preference that the poorly water-soluble drug is a steroid. Moreover, the '684 patent successfully exemplifies the preparation of nanoparticulate formulations of danazol, a steroid, using different surface stabilizers (e.g. PVP in Example 4, beginning at column 10, line 40). As is readily apparent from the chemical structures of danazol and beclomethasone dipropionate, both compounds share a common core cyclopent[a]phenanthrene structure. Thus, given the



very close structural similarity in the core structure of danazol and beclomethasone dipropionate the ordinary skilled artisan in view of the below cited prior art does have a reasonable expectation of successfully obtaining nanoparticulate formulations of beclomethasone, based on the demonstrated success in the '684 patent in obtaining nanoparticulate of danazol.

Additionally, post-filing art verifies the Examiner's position that there is a reasonable expectation of successfully obtaining nanoparticulate formulations of beclomethasone per the teachings of the '684 patent cited below and the other cited references. Thus, contrary to Dr. Liversidge's general statements, when drugs sharing the same or substantially similar core structure are compared, such as the twenty-two specific corticosteroids (e.g. beclomethasone dipropionate, cortisone, fluticasone propionate, mometasone, etc.), explicitly taught by U.S. Patent No. 8,003,127 as being suitable for the preparation of nanoparticulates, there is necessarily a reasonable expectation of successfully obtaining nanoparticulates of beclomethasone and other steroids. Thus, for the aforementioned reasons, Dr. Liversidge's declaration is found unpersuasive.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.
3. Ascertaining the differences between the prior art and the claims at issue, and resolving the level of ordinary skill in the pertinent art.

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4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

**Claims 28-36, 39-40, 51-60, and 64-73 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Liversidge et al. (U.S. Patent No. 5,145,684) in view of Pavord, I. et al. ("Pharmacokinetic optimisation of inhaled steroid therapy in asthma," *Clin. Pharmacokinet.*, 1993 Aug., 25(2), abstract only), "Glaxo History" (accessed on October 24, 2008 at [www/gsk.com/about/history-noflash.htm](http://www/gsk.com/about/history-noflash.htm)) ("Glaxo History") (of record), and the Merck Index, 10<sup>th</sup> Edition (Merck & Co., Inc.: Rahway, NJ, 1983, entry 1018 on page 144) ("MERCK"), as evidenced by Radhakrishnan (U.S. Patent No. 5,049,389) (of record) and Palmer (U.S. Patent No. 5,208,226).<sup>1</sup>**

#### *Applicant Claims*

Applicants claim a method treating a respiratory illness in a mammal comprising the steps of (a) providing an aerosol composition comprising aqueous droplets having a particle size of less than 10 microns in diameter, wherein the droplets comprise (i) water, (ii) crystalline particles of beclomethasone having an effective average particle size of

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<sup>1</sup> A copy of the complete Pavord reference is provided with this office action and is cited on the attached PTO-892.

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less than 1,000 nm (*i.e.* at least 90% of the particles have a weight average particle size of less than about 1,000 nm, as defined on pg. 16, lines 24-27 of Applicants' specification), (iii) at least one surface modifier adsorbed on the surface of the crystalline beclomethasone particles, and (b) administering the aerosol composition to the lungs of a mammal, wherein the respiratory disease is selected from the group consisting of asthma, emphysema, respiratory distress syndrome, chronic bronchitis, and cystic fibrosis.

*Determination of the Scope and Content of the Prior Art (MPEP §2141.01)*

Liversidge teaches that dispersible particles consisting essentially of crystalline poorly soluble drug substance having a surface modifier adsorbed on the surface thereof exhibit unexpectedly higher bioavailability (title; abstract; col. 1, lines 5-10; col. 2, lines 34-37; and col. 3, lines 3-9). The effective average particle size of the invented particles is less than about 400 nm (abstract; col. 2, lines 38-43; col. 5, lines 25-40; claims 1-5). The phrase "effective average particle size of less than about 400 nm" is defined to mean that at least 90% of the particles have a weight average particle size of less than about 400 nm (col. 5, lines 25-28). Preferably, at least 95% and more preferably, at least 99% of the particles have a particles size less than the effective average, such as 400 nm (col. 5, lines 33-37). In some embodiments, the effective average particle size is less than about 100 nm (col. 5, lines 30-34). Suitable crystalline poorly soluble drugs include anti-inflammatory agents and corticosteroids, and in preferred embodiments the drug substance is a steroid (col. 3, lines 53-64; col. 4, lines 25-27; and claims 4-5). The drug substances are commercially available or can be prepared by techniques known in the art (col. 4, lines 13-14). Suitable surface modifiers

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are disclosed from column 4, line 34 through col. 5, line 12 (*e.g.* sodium lauryl sulfate, lecithin, Pluronic F-68 [*i.e.* a polymer], etc.). The surface modifiers taught by Liversidge as being suitable are essentially ones recited in Applicants' laundry list in claim 32. For example, Liversidge **explicitly identifies polyvinyl alcohol as being a suitable surface modifier** (col. 4, line 55). **Suitable amounts of surface modifier are taught to be about 0.1-10 mg per square meter surface area of the drug substance (i.e. 0.1-90% w/w, preferably 20-60% w/w, based on the total weight of the dry particle)** (col. 7, lines 10-20).

Liversidge teaches **that the nanoparticles of crystalline drug substance may be obtained by conventional milling techniques, such as air jet and fragmentation milling** (col. 5, lines 50-61). Liversidge provides the necessary guidance to obtain nanocrystalline drug particles (see col. 5, line 41 through col. 7, line 29; claims 16-20). Liversidge teaches that the compositions may be delivered to mammals (*e.g.* claim 15).

Merck teaches that **both beclomethasone and its diester- beclomethasone dipropionate- are suitable for the treatment of asthma** (entry 1018 on page 144).

Glaxo history teaches that in 1972 a commercial product comprising the inhaled beclomethasone dipropionate steroid was launched by Glaxo as BECOTIDE® for the treatment of asthma. **BECOTIDE® is an aqueous suspension of beclomethasone dipropionate that is conventionally administered by nebulization** (*i.e.* it is atomized from a nebulizer) to treat bronchial asthma, which was commercially available at the time of the instant invention, as evidenced by Radhakrishnan (col. 5, lines 43-51). Radhakrishnan's teachings also evidence that beclomethasone dipropionate is **a poorly water-soluble active agent** (col. 4, lines 22-23).

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Pavord teaches that that the recognition that asthma has a large inflammatory component has led to the use of steroids in its treatment and the two most widely used steroidal agents to treat asthma are beclomethasone dipropionate and budesonide (abstract).

Palmer evidences that beclomethasone dipropionate is an anti-inflammatory corticosteroid (col. 1, lines 32-34).

*Ascertainment of the Difference Between Scope the Prior Art and the Claims  
(MPEP §2141.012)*

Liversidge lacks the teaching of specific corticosteroids. This deficiency is cured by the teachings of Pavord, Merck, and Glaxo History, as evidenced by Radhakrishnan and Palmer.

*Finding of Prima Facie Obviousness Rationale and Motivation  
(MPEP §2142-2143)*

It would have been prima facie obvious to modify the teachings of Liversidge to utilize beclomethasone as a corticosteroid (Palmer), anti-inflammatory (Palmer), or steroid (Palmer, Pavord, and Glaxo) selected to prepare nanoparticulate dispersions, because Liversidge explicitly indicates that suitable active agents include poorly water soluble anti-inflammatory agents, corticosteroids, and steroids and Pavord establishes that at the time of Applicants' claimed invention beclomethasone was one of the two most widely used anti-inflammatory steroids in the treatment of asthma. Furthermore, beclomethasone satisfies the requirement in Liversidge that the selected active agent is poorly water-soluble (Radhakrishnan). Thus, Liversidge and Pavord provide ample

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motivation for the ordinary skilled artisan to select beclomethasone as an active agent used to make nanoparticulate pharmaceutical suspensions commensurate in scope with Liversidge's teachings. Regarding the preparation of aqueous suspensions of beclomethasone an ordinary skilled artisan would have been motivated to obtain aqueous suspensions of nanoparticulate crystalline beclomethasone per Liversidge's teachings, because at the time of the instant invention beclomethasone was commercially available as an aqueous suspension marketed under the BECOTIDE® trademark and sold by Glaxo ("Glaxo History"). The BECOTIDE® product was known to contain beclomethasone dipropionate at a concentration of 50 micrograms/ml, as evidenced by Radhakrishnan. An ordinary skilled artisan would have been further motivated to use Liversidge's technology to obtain crystalline nanoparticulate beclomethasone aqueous suspensions, because said suspensions would be reasonably expected to exhibit greater local bio-availability of the beclomethasone (Liversidge) and would reasonably be expected to reach a patient's alveoli upon inhalation of an aqueous suspension of nanoparticulate crystalline beclomethasone, due to the small size of the suspended crystalline beclomethasone.

Regarding particle size of the crystalline beclomethasone and the amount of surfactant, the combined prior art teaches overlapping ranges. A prima facie case of obviousness necessarily exists when the prior art range overlaps or touches a claimed range, such as in the instant rejection. MPEP § 2144.05. Regarding the amount of beclomethasone suspended in the formulation, the commercially available BECOTIDE® product contained a concentration of beclomethasone dipropionate of 0.05% w/w, which reads on an amount of beclomethasone of about 0.1% w/w as recited in dependent claim

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39. Concerning the amount of beclomethasone recited in Applicants' dependent claim 40, it is the Examiner's position that the ordinary skilled artisan would have been motivated to modify (i.e. increase or decrease) the concentration of beclomethasone based upon a patient's response to a particular dosage of beclomethasone therapy. Thus, it would have been *prima facie* obvious to utilize different dosages, and the ordinary skilled artisan would have arrived at dosage of from about 5% to about 30% w/w as is recited in Applicants' claim 40. Absent some demonstration of unexpected results from the claimed dosage range, the optimization of the amount of beclomethasone would have been obvious at the time of applicant's invention.

Regarding the recitation of beclomethasone and not beclomethasone dipropionate, the ordinary skilled artisan would consider the beclomethasone to be interchangeable with beclomethasone dipropionate, because both compounds are known to be suitable for the treatment of asthma, are poorly water-soluble, and are anti-inflammatory corticosteroids. Applicants' tabulated specification data is noted, and it does not demonstrate any unexpected or surprising results. Dr. Bosch's declaration data is noted, but is found unpersuasive for the reasons set forth above.

Regarding claim 73, Liversidge explicitly identifies polyvinyl alcohol as being a suitable surface modifier. Consequently, it would have been *prima facie* obvious to select polyvinyl alcohol as the surface modifier. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

***Response to Arguments***

Applicant's arguments filed February 12, 2012 have been fully considered but they are not persuasive. Applicants traverse the rejection by (i) arguing that Dr. Liversidge's declaration establishes that at the time of the claimed invention there was no reasonable expectation of successfully obtaining nanoparticulate formulations of beclomethasone, because of examples of failed attempts of making nanoparticulate formulations of chemical dissimilar drugs; (ii) Liversidge is allegedly incorrectly identified as the closest prior art, which Applicants allege is VANCERIL® aerosol formulation comprising a suspension of beclomethasone dipropionate in propellants; and (iii) allegedly the Bosch declaration submitted on March 31, 2011 is commensurate in scope with Applicants' claims.

Regarding (i), the Liversidge declaration has been addressed above. The Office's evaluation of the Liversidge reference and conclusion that it is unpersuasive are herein incorporated by reference. It is emphasized that within the four corners of the Liversidge declaration Dr. Liversidge failed to address the teaching of the cited '684 patent and whether there would have been a reasonable expectation of successfully obtaining nanoparticulate formulations of beclomethasone given that the '684 patent successfully demonstrated the successful preparation of several nanoparticulate steroid formulations of danazol, which is structurally similar to beclomethasone and shares a common core structure. Instead Dr. Liversidge made broad conclusions supported by comparing pharmaceuticals that are structurally dissimilar, unlike the facts of the instant rejection which are based in part on the explicit teachings of the '684 patent identifying corticosteroids (i.e. beclomethasone is a corticosteroid and necessarily a steroid) as

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suitable for the preparation of nanoparticulate formulations and the demonstration of the successful preparation of nanoparticulate formulations of danazol a steroid that shares a common core structure with beclomethasone and other corticosteroids.

Regarding (ii), Applicants and this Examiner have respectfully reached an impasse. Applicants' arguments that VANCERIL® is the closest prior art to the claimed invention is an erroneous assertion. Applicants assert that VANCERIL® comprises the same active agent and is of the **same dosage form**. Applicants are correct that the active agent in VANCERIL® and the rejected claims is the same; but, Applicants are mistaken that the dosage forms are the same. Applicants' claims recite **aqueous** suspensions of beclomethasone, whereas VANCERIL® is a **propellant** suspension. These two dosage forms are different dosage forms. Applicants are directed to the teachings of Wu et al. (Exhibit 4 of Dr. Liversidge's declaration) at page 12, lines 822-825 and 858, wherein Wu explicitly notes that little is understood about solvation in low di-electric HFA media (i.e. propellant media) which makes the selection of stabilizers or stabilizer combinations burdensome, explicitly distinguishes aqueous and non-aqueous dispersion media, and states that the particular dispersion medium is an important factor in obtaining stable suspensions. Compared to HFA propellants, water is a much higher di-electric solvent. Thus, based on the differences between aqueous and propellant dispersion media and the much poorer understanding of solvation in propellant media compared to aqueous media, to assert that an aqueous suspension of beclomethasone is an identical dosage form compared to the non-aqueous propellant suspension of beclomethasone in the VANCERIL® product is a factual mischaracterization.

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Liversidge is the closest prior art, because it teaches the same kind of nanoparticulates (i.e. nanoparticles of poorly water-soluble drugs) having a surface modifier adsorbed to the surface thereof. In fact, Liversidge explicitly identifies corticosteroids and preferably steroids as examples of suitable poorly water-soluble drugs that can be obtained as nanoparticles having a surface modifier adsorbed to the surface thereof. The combined prior art establishes that it was conventional at the time of the claimed invention to administer aqueous suspensions of corticosteroids, such as beclomethasone dipropionate, to treat asthma. Thus, the use of Liversidge's teachings to obtain aqueous suspensions of nanoparticulate beclomethasone dipropionate having a surface modifier adsorbed to the surface thereof is *prima facie* obvious.

Regarding (iii), the Office's evaluation of the second Bosch declaration filed on March 31, 2011 and finding that this declaration is unpersuasive, is herein incorporated by reference from the office action mailed on October 26, 2011. Applicants also assert that the Bosch declaration allegedly establishes a trend that can be extrapolated to all surface stabilizers at all concentrations. This is unpersuasive. As explained in the October 26, 2011 office action, the Bosch declaration is limited to the evaluation of formulations wherein the surface stabilizer is polyvinyl alcohol (PVAL), which is structurally dissimilar from the other surface stabilizers recited, for example, in Applicants' dependent claims 32 and 74. To date Applicants have provided no additional evidence that would permit the ordinary skilled artisan to reasonably extrapolate from the limited showing in the Bosch declaration for beclomethasone/PVAL nanoparticulate formulations to other beclomethasone formulations using one or more structurally dissimilar surface modifiers. If Applicants believe Dr. Liversidge's declaration

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statements regarding the challenges of selecting a suitable surface stabilizer for successfully obtaining nanoparticulate formulations, which their arguments indicate they do, then it is disingenuous for them to also assert that the demonstration of the successful preparation of beclomethasone nanoparticles using only PVAL provides a basis for the ordinary skilled artisan to reasonably extrapolate the limited results to every other possible surface stabilizer. The rejection is maintained.

**Claims 42-43 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Liversidge et al. (U.S. Patent No. 5,145,684) in view of Pavord, I. et al. ("Pharmacokinetic optimisation of inhaled steroid therapy in asthma," *Clin. Pharmacokinet.*, 1993 Aug., 25(2), abstract only), "Glaxo History" (accessed on October 24, 2008 at [www/gsk.com/about/history-noflash.htm](http://www/gsk.com/about/history-noflash.htm)) ("Glaxo History") (of record), and the Merck Index, 10<sup>th</sup> Edition (Merck & Co., Inc.: Rahway, NJ, 1983, entry 1018 on page 144) ("MERCK"), as evidenced by Radhakrishnan (U.S. Patent No. 5,049,389) (of record) and Palmer (U.S. Patent No. 5,208,226) as applied to claims 28-36, 39-40, 51-60, and 64-73 above, and further in view of Spear et al. (U.S. Patent No. 5,525,623).**

#### *Applicant Claims*

Applicants claim a method treating a respiratory illness in a mammal as described above, wherein the nebulizing step is done using a jet nebulizer (claim 42) or an ultrasonic nebulizer (claim 43).

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***Determination of the Scope and Content of the Prior Art (MPEP §2141.01)***

The teachings of Liversidge, Pavord, Glaxo History, Merck, Radhakrishnan, and Palmer are set forth above.

Spear teaches that jet nebulizers and ultrasonic nebulizers are conventional means of creating aerosols for use as asthma medication (col. 13, lines 34-40).

***Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)***

Liversidge lacks the teaching of a jet nebulizer or an ultrasonic nebulizer. These deficiencies are cured by the teachings of Spear.

***Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)***

It would have been prima facie obvious at the time of the instant invention to nebulize an aqueous solution comprising beclomethasone dipropionate (BDP) using either an ultrasonic nebulizer or a jet nebulizer, because both nebulizers were conventionally used to administer pharmaceutical aqueous formulations. An ordinary skilled artisan would have been motivated and would have had a reasonable expectation of nebulizing an aqueous pharmaceutical formulation, such as that resulting from the teachings of Liversidge and Radhakrishnan, with a jet nebulizer or an ultrasonic nebulizer, because said nebulizers were conventionally known to be suitable for the inhalation administration of aqueous pharmaceutical formulations and were conventionally used for this purpose (Spear). The use of a device in the matter in which said device was intended to be used is prima facie obvious. Therefore, the claimed

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invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

### ***Response to Arguments***

Applicant's arguments filed February 10, 2012 have been fully considered but they are not persuasive. Applicants traverse the rejection by reiterating the arguments presented against the first rejection under §103(a) maintained above, attacking the references individually, and that the office has provided no rationale for combining the cited references because Spears allegedly teaches that only solutions are administered by the use of jet nebulizers or ultrasonic nebulizers. The Office's above rebuttal of Applicants' arguments is herein incorporated by reference. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

The Office has provided ample rationale for combining the cited teachings, and Applicants desire to believe otherwise does not make it so. Additionally, Applicants are misreading the cited portion of Spears. Spears statement cannot be fairly construed, as Applicants imply, to mean that jet nebulizers and ultrasonic nebulizers can only be used to administer solutions. Rather, Spears statements indicates that the use of **any of the conventional means of generating aerosols** such as metered dose inhalers, jet nebulizers, and ultrasonic nebulizers may be used to administer Spears' solution

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formulations. Using Applicants' strained reading of the cited portion of Spears, one would be surprised to read that the prior art MDI formulation of VANCERIL®, which Applicants admit is a MDI suspension formulation of beclomethasone, can be used to administer suspensions. Given that Applicants readily concede that VANCERIL® is a propellant suspension formulation, it is clear that Applicants' interpretation of the cited portion of Spears is a misreading of Spears' statement. The rejection is maintained.

**Claim 74 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Liversidge et al. (U.S. Patent No. 5,145,684) in view of Pavord, I. et al. ("Pharmacokinetic optimisation of inhaled steroid therapy in asthma," *Clin. Pharmacokinet.*, 1993 Aug., 25(2), abstract only), "Glaxo History" (accessed on October 24, 2008 at [www/gsk.com/about/history-noflash.htm](http://www/gsk.com/about/history-noflash.htm)) ("Glaxo History") (of record), and the Merck Index, 10<sup>th</sup> Edition (Merck & Co., Inc.: Rahway, NJ, 1983, entry 1018 on page 144) ("MERCK"), as evidenced by Radhakrishnan (U.S. Patent No. 5,049,389) (of record) and Palmer (U.S. Patent No. 5,208,226) as applied to claims 28-36, 39-40, 51-60, and 64-73 above, and further in view of June (EP 0602701 A1) (cited on the August 13, 2000 IDS).**

#### *Applicant Claims*

Applicants claim a method treating a respiratory illness in a mammal as described above, wherein the surface stabilizer of the recited composition is tyloxapol.

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***Determination of the Scope and Content of the Prior Art (MPEP §2141.01)***

The teachings of Liversidge, Pavord, Glaxo History, Merck, Radhakrishnan, and Palmer are set forth above.

June teaches **the use of tyloxapol as a nanoparticulate stabilizer and dispersant** for use with compositions comprising nanoparticulate diagnostic or **therapeutic agents** (title; abstract; col. 1, lines 15-41; col. 3, lines 41-49; and claim 1). **Tyloxapol is taught to be an excellent wetting agent** and that it affords enhanced blood pool residence via reduced macrophage uptake (col. 1, lines 26-30). Suitable amounts of tyloxapol are taught to range from about 0.1 to 90% w/w (col. 9, lines 52-56). The tyloxapol formulations may be administered topically and **formulations for topical administration include inhalants** (col. 7, lines 1-6 and col. 8, lines 51-53). Tyloxapol may function as a surface modifier, stabilizer, dispersant, or combination of the three (col. 3, lines 41-49).

***Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)***

Liversidge lacks the teaching of nanoparticulate formulations of poorly water-soluble drugs, wherein the surface stabilizer adsorbed to the surface of the poorly-water soluble drug nanoparticulates is tyloxapol. This deficiency is cured by the teachings of June.

***Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)***

It would have been prima facie obvious at the time of the instant invention to select tyloxapol as the surface stabilizer in Liversidge's formulations, because it is known

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to be suitable in the preparation of nanoparticulate therapeutic agents (June). Additionally, an ordinary skilled artisan would have been motivated to select tyloxapol as the surface stabilizer or one of the surface stabilizers used to obtain poorly-water soluble drug nanoparticulate formulations, because it exhibits excellent wetting properties (June). Accordingly, the ordinary skilled artisan would have had a reasonable expectation of successfully obtaining poorly-water soluble drug nanoparticulate formulations using tyloxapol as a surface stabilizer. The analysis of Applicants' Bosch declaration is set forth above and herein incorporated by reference. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

### ***Response to Arguments***

Applicant's arguments filed February 10, 2012 have been fully considered but they are not persuasive. Applicants traverse the rejection by reiterating the arguments presented against the first rejection under §103(a) maintained above, and arguing that the Bosch declaration allegedly demonstrated unexpected results for nanoparticulate formulations of beclomethasone with tyloxapol as the surface stabilizer adsorbed to the surface of the beclomethasone nanoparticles.

The Office's above rebuttal of Applicants' arguments is herein incorporated by reference. The Examiner notes that there are only two declarations of record from Dr. Bosch, which were submitted on August 30, 2010 (Bosch Declaration #1) and March 31, 2011 (Bosch Declaration #2). Neither Bosch declaration of record described any results

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for nanoparticulate formulations of beclomethasone with tyloxapol as the adsorbed surface stabilizer. Both Bosch declarations are limited to the discussion of nanoparticulate formulations of beclomethasone with polyvinyl alcohol as the surface stabilizer (See ¶ 5 of the August 30, 2010 and March 31, 2011 Bosch declarations). Thus, Applicants' arguments concerning demonstrated unexpected results for nanoparticulate formulations of beclomethasone with tyloxapol as the adsorbed surface stabilizer are unpersuasive. The rejection is maintained.

### ***Double Patenting***

The previous provisional obviousness-type double patenting rejections over copending Application Nos. 10/035,324 and 12/292,092 **are withdrawn**, because these copending applications were abandoned on February 14, 2012 and December 20, 2011, respectively. Consequently, these provisional obviousness-type double patenting rejections **are now moot**.

### ***Conclusion***

**Claims 28-36, 39-40, 42-43, 51-60, and 64-74 are rejected. No claims are allowed.**

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within

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TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James H. Alstrum-Acevedo whose telephone number is (571) 272-5548. The examiner is on a flexible work schedule, but can normally be reached Monday-Friday from ~10:00 AM EST to 6:00 pm EST and on Saturdays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on (571) 272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/JAMES H. ALSTRUM-ACEVEDO/  
Primary Examiner, Art Unit 1616  
Technology Center 1600